14

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
GM5084		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US00/12392	05/05/2000	07/05/1999
International Patent Classification (IPC) or national classification and IPC C12N15/12		
Applicant THE GOVERNMENT OF THE UNITED STATES OF AM...et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
06/12/2000	17.07.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Huber, A Telephone No. +49 89 2399 8173

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US00/12392

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-51 as originally filed

Claims, No.:

1-39 as originally filed

Drawings, sheets:

1/13-13/13 as originally filed

Sequence listing part of the description, pages:

1-2, as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☒ contained in the international application in written form.
- ☒ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 23, 25, 27-31 (IA).

because:

   ☒ the said international application, or the said claims Nos. 23, 25, 27-31 (IA) relate to the following subject matter which does not require an international preliminary examination (*specify*):
   see separate sheet

   ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US00/12392

1. Statement

Novelty (N)	Yes:	Claims	6, 7, 9, 10, 13-15, 21, 22, 38, 39
	No:	Claims	1-5, 8, 11, 12, 16-20, 23-37
Inventive step (IS)	Yes:	Claims	
	No:	Claims	6, 7, 9, 10, 13-15, 21, 22, 38, 39
Industrial applicability (IA)	Yes:	Claims	1-22, 24, 26, 32-39
	No:	Claims	

2. Citations and explanations
see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 25, 29, 30 and Claims 23, 27, 28 and 31, insofar as in vivo application is concerned, relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

For the assessment of the above claims on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. The present application relates to viral vectors (retroviral, adenoviral) carrying genes encoding antiangiogenic proteins.
   Exemplified is an adenoviral vector comprising the endostatin gene.

2. Reference is made to the following documents:

   D1: WO 98 49321 A (LI HONG;LU HE; RAGOT THIERRY; YEH PATRICE; GRISCELLI FRANC; LEGRAND YV) 5 November 1998 (1998-11-05)
   D2: TANAKA T. ET AL.: 'VIRAL VECTOR-TARGETED ANTIANGIOGENIC GENE THERAPY UTILIZING AN ANGIOSTATIN COMPLEMENTARY DNA'

CANCER RESEARCH, vol. 58, no. 15, 1 August 1998 (1998-08-01), pages 3362-3369, XP000857409 ISSN: 0008-5472

D3: BRAMSON J. L. ET AL.: 'Direct intratumoral injection of an adenovirus expressing Interleukin-12 induces regression and long-lasting immunity that is associated with highly localized expression of Interleukin-12' HUMAN GENE THERAPY, vol. 7, 20 October 1996 (1996-10-20), pages 1995-2002, XP002093895 ISSN: 1043-0342

D4: TANAKA T. ET AL.: 'Viral vector-mediated transduction of a modified platelet factor 4 cDNA inhibits angiogenesis and tumor growth.' NATURE MEDICINE, vol. 3, no. 4, 1997, pages 437-442, XP002145430 ISSN: 1078-8956

D5: SCHWARZ M. ET AL.: 'EMAP II: A modulator of neovascularization in the developing lung.' AMERICAN JOURNAL OF PHYSIOLOGY, vol. 20, no. 2, February 1999 (1999-02), pages L365-L375, XP002145431 ISSN: 1081-5589

D6: PIKE S. E. ET AL.: 'Vasostatin, a calreticulin fragment, inhibits angiogenesis and suppresses tumor growth.' JOURNAL OF EXPERIMENTAL MEDICINE, vol. 188, no. 12, 21 December 1998 (1998-12-21), pages 2349-2356, XP002145432 ISSN: 0022-1007

D7: WO 97 34586 A (TSIARAS WILLIAM G ;SPEAR PETER D (US); BAETGE E EDWARD (US); CYTOT) 25 September 1997 (1997-09-25)

D8: SHUTTLEWORTH C. A.: 'Type VIII collagen.' INTERNATIONAL JOURNAL OF BIOCHEMISTRY & CELL BIOLOGY, vol. 29, no. 10, October 1997 (1997-10), pages 1145-1148, XP000938722 ISSN: 1357-2725

D9: RAMCHANDRAN R. ET AL.: 'Antiangiogenic activity of restin, NC10 domain of human collagen XV: Comparison to endostatin.' BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, vol. 255, no. 3, 24 February 1999 (1999-02-24), pages 735-739, XP002145434 ISSN: 0006-291X

D10: RAMCHANDRAN R. ET AL.: 'Cloning, expression of a novel anti-angiogenic protein: Restatin.' PROCEEDINGS OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH, vol. 40, March 1999 (1999-03), page 620 XP000938553 ISSN: 0197-016X

D11: BLEZINGER P. ET AL.: 'SYSTEMIC INHIBITION OF TUMOR GROWTH AND TUMOR METASTASES BY INTRAMUSCULAR ADMINISTRATION OF THE

ENDOSTATIN GENE' NATURE BIOTECHNOLOGY, vol. 17, no. 4, April 1999 (1999-04), pages 343-348, XP000857410 ISSN: 1087-0156 cited in the application

3. All of the documents D1 to D4 disclose viral vectors comprising antiangiogenic proteins.
In D1, for instance, a replication deficient adenovirus vector comprising a gene encoding an antiangiogenic factor (e.g.angiostatin, urokinase) is disclosed. Further antiangiogenic proteins are mentioned to be useful in the invention (thrombospondin, endostatin). The vector is useful for inhibiting tumour growth. D1 is novelty-destroying for the subject-matter of Claims 1-5, 8, 11, 16-20 and 23-37.
Also D2 discloses viral-vector targeted antiangiogenic gene therapy by introducing angiostatin cDNA into a retroviral or adenoviral vector. It affects therefore the novelty of Claims 1-3, 8, 16-20 and 23-37.
D3 relates to adenoviral vectors comprising IL-12 for the treatment of tumours, thus destroying the novelty of Claims 1, 2, 11, 16, 18 and 23-31, while D4 shows that viral vector mediated transduction of platelet factor 4 inhibits angiogenesis and tumour growth (Claims 1-3, 5, 8, 12, 16-20, 23-31 and 37).
Consequently, the subject-matter of Claims 1-5, 8, 11, 12, 16-20, 23-37 is not novel in view of the above documents (Art. 33(2) PCT).

D11 discloses the expression of antiangiogenic factors (endostatin) fused to a signal sequence. Said document is therefore novelty-destroying for Claim 37.

4. EAMP-II, vasostatin, vasculostatin, collagen VIII, the NC10 domain of collagen XV, restatin and IP-10 are known as antiangiogenic factors (see D5, D6, D7, D8 and D9 and D10). To employ any of these in a viral vector according to e.g. D1 would be obvious to the skilled person and does not require inventive skills. The subject-matter of Claims 6, 7, 9, 10, 13, 14 and 15 does therefore not involve the required inventive step (Art. 33(3) PCT).

The use of an adenoviral signal sequence is not disclosed in the prior art. There

is, however, no indication in the decription, that the use of the specifically claimed signal sequence brings about any unpredictable advantages in comparison to other signal sequences which were used in the cited prior art. Since the subject-matter of Claims 21, 22, 38 and 39 does not appear to be associated with a specific technical effect, no inventive step can be acknowledged for the subject-matter of said claims (Art. 33(3) PCT).